33. (Amended) The conjugate of claim 1, wherein the covalent structure of the conjugate is free of any matter other than the antibody fragment and PEG [nonproteinaceous polymer] molecules that form the conjugate.

34. (Amended) The conjugate of claim 1, wherein the covalent structure of the conjugate incorporates one or more nonproteinaceous labels, and wherein the covalent structure of the conjugate is free of any matter other than the antibody fragment, PEG [nonproteinaceous polymer] and nonproteinaceous label molecules that form the conjugate.

Please add the following new claim.

--36. The conjugate of claim 1, wherein the second cysteine residue is substituted with a serine residue in the first opposite chain.--

REMARKS

Claims 1-35 are pending in the application. Claims 8-18, 23-25 and 30 are canceled and new claim 36 is added. Claims 2-4, 6, 7, 20, 22 and 27 are withdrawn from further consideration as being drawn to nonelected species. Accordingly, claims 1, 5, 19, 21, 26, 28, 29 and 31-36 are under examination in the case. Applicants respectfully request reconsideration of the outstanding rejections for the reasons that follow.

Claim Amendments

Claim 1 is amended to recite a "conjugate consisting essentially of a single antibody fragment, wherein the antibody fragment is covalently attached to a single polyethylene glycol (PEG) molecule, wherein the antibody fragment is a Fab' comprising (1) a first chain that is either a light chain or a heavy chain and (2) a first opposite chain that is either a heavy chain opposite the first light chain or a light chain opposite the first heavy chain, wherein the PEG molecule is covalently attached to a first cysteine residue in the first chain that would ordinarily form a disulfide bridge with a second cysteine residue in the first opposite chain, wherein the disulfide bridge is avoided by the substitution of another amino acid residue for the second cysteine residue in the first opposite chain, wherein the apparent size of the conjugate is at least about 500 kD", as supported, at least, on page 35, line 28 to page 36, line 5 and page 43, lines 2-4 of the specification, and in original claims 1, 14,15, 16 and 18.

Claims 5-7, 19, 26, 27, 33 and 34 are amended to be consistent with amended claim 1.

New claim 36 recites the "conjugate of claim 1, wherein the second cysteine residue is substituted with a serine residue in the first opposite chain", as supported, at least, on page 35, line 28 to page 36, line 5 of the specification.

No new matter is believed to be added by the present claim amendments.

Election of Species

Applicants confirm the provisional election without traverse of the following species:

(1) The species of a conjugate containing one or more Fab' fragments attached to no more than 10 nonproteinaceous polymer molecules, which species has an apparent size of at least about 500 kD and which species has an apparent size that is at least about 8 fold greater than the apparent size of at least one Fab' fragment contained in the conjugate.

(2) The species of a conjugate that contains a PEG molecule that is a single chain molecule having an average molecular weight of at least about 20 kD.

Claims 1, 5, 19, 21, 26-29, and 31-36 are readable upon the elected species.

Applicants specifically reserve their rights to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. §1.141.

Information Disclosure Statements

The Office indicates that Applicant's Information Disclosure Statements filed on December 15, 1999, October 22, 1999 and May 26, 1999 fail to comply with the provisions of 37 C.F.R. §§1.97-98 and MPEP §609 because copies of the references cited were not provided by Applicants. Although Applicants believe that the Information Disclosure Statements in question were filed with a copy of every cited reference, Applicants herewith submit a Third Supplemental Information Disclosure Statement (which lists all references cited in the earlier Information Disclosure Statements) along with copies of all of the references that are apparently missing from the Office's files.

Drawing Informalities

The Office notes that the application was filed with informal drawings, and that color photographs will only be accepted upon Applicants' compliance with the applicable rules.

Applicants acknowledge the drawing informalities noted by the Office and intend to remedy such informalities upon receiving a notice of allowable subject matter from the Office.

The Office objects to the disclosure on grounds that there are no Y-axis figure legends appearing in Figs. 34C-34D, 39, 40, 50A-50B, 55A-55C or 58A-58B. Applicants herewith amend the drawings to include the figure legend "Neutrophil Migration Index" on the Y-axis appearing in each of Figs. 34A-34D, 39, 40, 50A-50B, 55A-55C and 58A-58B. The amended figure legends are consistent with those appearing in Fig. 6 and Fig. 7. The data shown in Figs. 6, 7, 34A-34D, 39, 40, 50A-50B, 55A-55C and 58A-58B were generated using the neutrophil chemotaxis inhibition assay procedure essentially as described in Example B.2 (on page 189, line 8 to page 190, line 7 of the specification). Thus, no new matter is believed to be added by the present amendment to the drawings.

Priority Claim

The Office apparently finds that the amino acid sequence of SEQ ID NO:62 recited in claim 29 is not disclosed in parent application U.S. Ser. No. 60/074,330, filed January 22, 1998, or in parent application U.S. Ser. No. 60/075,467, filed February 20, 1990. Thus, the Office determines that claim 29 is not entitled to the benefit of the filing date of either U.S. Ser. No. 60/074,330 or U.S. Ser. No. 60/075,467.

Applicants respectfully point out that the amino acid sequence of SEQ ID NO:62 is disclosed in Fig. 45 of parent application U.S. Ser. No. 60/074,330 as filed and in Fig. 45 of parent application U.S. Ser. No. 60/075,467 as filed. The amino acid sequence disclosed in Fig. 45 of the parent applications is the same as the amino acid sequence (SEQ ID NO:62) disclosed in Fig. 45 of the present application. Accordingly, claim 29 is entitled to the benefit of the January 22, 1998 and February 20, 1998 filing dates of parent applications U.S. Ser. Nos. 60/047,330 and 60/075,467, respectively. Applicants respectfully request confirmation from the Office that claim 29 is entitled to the benefit of the January 22, 1998 and February 20, 1998 filing dates of parent applications U.S. Ser. Nos. 60/047,330 and 60/075,467, respectively.

Specification Informalities

The Brief Description of the Drawings section of the specification does not correctly reflect the panels of Fig. 48. While Fig. 48 contains panels A-Z, the text in question refers to Figs. 48A-48T. Applicants herein amend the text in question to refer to Figs. 48A-48Z. No new matter is believed to be added hereby.

Rejection under 35 U.S.C. §112, first paragraph

1. Written Description

Claims 1, 5, 10, 18, 19, 21 and 30-35 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed subject matter. In particular, the Office finds that the claims encompass conjugates that do not bind to antigen and that the specification fails to adequately disclose such conjugates.

Applicants respectfully traverse the rejection. Applicants submit that the disclosure of the specification would have conveyed to the practitioner that the inventors were in possession of the entire scope of the claimed invention, including conjugates that may exhibit no binding to antigen.

On page 94, lines 10-20, the specification discloses reagent uses of the claimed conjugates, which include the use of the conjugate to induce tolerance for the underivatized parental antibody fragment in a test animal. The specification refers the practitioner to Wie, et al., Int. Archs. Allergy Appl. Immunol., 64: 84-99 (1981), of record, hereafter "Wie," for a description of how to use PEGylated allergen for the induction of tolerance to underivatized allergen in an animal. In this application of the claimed invention, the conjugate serves only to prepare the test animal for use in characterizing the behavior of the underivatized parental antibody fragment free from any immune interference directed against the parental antibody fragment in the test animal. Thus, the toleragenic properties of the claimed conjugate allow the practitioner to prepare the test animal for use in experimental methods that require repeated inoculation of the animal with the parental antibody fragment.

The practitioner would have known that the ability of the conjugate to induce tolerance in the test animal as described in the specification is not dependent upon the antigen binding activity of the conjugate. In fact, Wie indicated that it is preferable for toleragens to exhibit no allergenicity (see the sentence bridging the columns on page 93 of Wie). In other words, the conjugate will function best as a toleragen if it does not react with antibody in the test animal. Thus, the practitioner would have actually preferred to use a conjugate that does not present epitopes recognizable by immune effector functions (including epitopes in the antigen-binding site of the antibody fragment) for the induction of tolerance in a test animal as described in the specification.

Since the ability of the claimed conjugate to bind antigen is not needed for the

conjugate to function as a toleragen according to the above-described application of the conjugate, the practitioner would have understood that the inventors had possession of the entire scope of the claimed invention, including conjugates that do not bind antigen, based on the disclosure of the application. Therefore, Applicants submit that the claims satisfy the written description requirement of 35 U.S.C. §112, first paragraph and respectfully request reconsideration and withdrawal of the rejection.

2. Enablement

Claims 1, 5, 10, 18, 19, 21 and 30-35 are rejected under 35 U.S.C. §112, first paragraph because the specification allegedly does not provide enablement for a conjugate that does not bind antigen. In addition, the Office apparently contends that the specification fails to provide the practitioner with sufficient guidance on how to produce conjugates of the invention which have antigen-binding activity without undue experimentation.

Applicants respectfully traverse the rejection. As shown in the discussion of the §112 written description rejection above, the specification would have enabled the practitioner to make and use conjugates having no antigen-binding activity for use as toleragens in test animals. Since antigen-binding activity is not needed for use of the conjugate as a toleragen, the application would have enabled the practitioner to make and use as toleragens all conjugates encompassed by the claimed invention, including conjugates that do not bind antigen.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §112, second paragraph

Claims are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

1. Rejection based on "consisting essentially of" language

The Office finds that the use of the language "consisting essentially of" renders the claims indefinite because it is unclear what other elements are encompassed that would not effect the basic and novel characteristics of the claimed invention. The Office apparently considers the "consisting essentially of" term indefinite when used in a compound claim.

Although Applicants do not necessarily agree with the rejection, Applicants have

amended claim 1 (and necessarily also claims 5, 19, 21, 26, 28, 29 and 31-35 depending therefrom) to specify a conjugate "consisting essentially of" a single antibody fragment that is a Fab' covalently attached to a single PEG molecule at a unique site on the Fab' molecule. The language "consisting essentially of" in a composition claim excludes ingredients that would materially affect the basic and novel characteristics of the claimed composition (Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 224 U.S.P.Q. 409, 412 (CAFC 1984)). As amended, the basic characteristics of the claimed invention are the single Fab' fragment, the single PEG molecule, and the unique site in the Fab' molecule specified for PEG derivatization. Thus, any modification of the claimed conjugate that would change the unique site for PEG derivatization, the number or type of antibody fragments (i.e. a single Fab' fragment), or the number or type of nonproteinaceous polymers (i.e. a single PEG molecule) specified in the claims would change the basic characteristics of the claimed invention. Accordingly, the "consisting essentially of" term satisfies the §112, second paragraph definiteness requirement in the context of amended claim 1 (and depending claims 5, 19, 21, 26, 28, 29 and 31-35).

2. Rejection based on "apparent size" and "at least about" language

The Office finds that the use of the language "apparent size" in the claims is indefinite allegedly because it is not clear what deviations from the molecular weight of "at least about 500 kD" are encompassed by the claims.

Applicants respectfully traverse the rejection.

It is settled law that imprecise terms can serve to reasonably describe the claimed subject matter to those of skill in the field of invention, and to distinguish the claimed subject matter from the prior art, thereby meeting the requirements of 35 U.S.C. §112, second paragraph (Andrew Corp. v. Gabriel Electronics, 6 USPQ2d 2010, 2012 (Fed. Cir. 1988)). In Modine Manufacturing Co. v. International Trade Commission, 37 USPQ2d 1609 (Fed. Cir. 1996), the court interpreted the claim term "relatively small" to mean "about 0.015-0.040 inch" with respect to the hydraulic diameter of condenser tubes because the text of the specification described the invention in terms of "a range of hydraulic diameters of about 0.015 inches to about 0.040 inches", overruling the lower court's holding that the subject claims are indefinite unless "relatively small" is construed as "precisely 0.040 inch". The court found that "patentability [of the subject claims] did not require an exact numerical limit of the hydraulic diameter" and that "[m]athematical precision should not be imposed for its own sake; a patentee has the right to claim the invention in terms that would be understood by persons of skill in the field of the invention" (37 PQ2d at 1617), citing Shatterproof Glass Corp. v.

Libbey-Owens Ford Co., 225 USPQ 634 (Fed. Cir. 1985) ("if the language is as precise as the subject matter permits, the courts can demand no more").

Under the law of Andrew Corp. v. Gabriel Electronics and Modine Manufacturing Co. v. International Trade Commission, the use of the term "about" in connection with the term "apparent size" in the present claims meets the requirements of 35 U.S.C. §112, second paragraph. As used herein, the term "about" raises no issue with respect to patentability over the cited art. Like the description of the invention in terms of "about 0.015-0.040 inch" in the specification of the Modine Manufacturing patent, the terms "at least about 500 kD" (in present claim 1), "at least about 800 kD" (in present claim 2), "at least about 1,400 kD" (in present claim 3) and "at least about 1,800 kD" (in present claim 4) are used throughout the present specification to describe the embodiments of Applicants' invention. Finally, the language describing the concentration elements in the present claims is as precise as the subject matter of Applicants' invention permits.

In the Modine Manufacturing patent, the court found that the hydraulic diameter of condenser tubes was subject to variability based on the nature of the coolant used and on the precision of measurement in the art (37 PQ2d at 1615). The court held that persons of ordinary skill in the art would have understood these factors and could have applied them to ascribe a reasonable meaning to the term "about" in the context of the Modine Manufacturing invention. Similarly, the practitioner of ordinary skill in the art would have known that certain variations in apparent size are inherent in the nature of Applicants' invention and that such variations are encompassed by the term "about" as used in the context of the apparent size parameters recited in the present claims. For example, the present invention contemplates the use of PEG molecules which exist in populations that are not completely uniform in molecular weight. Instead, commercially available PEG preparations are characterized by an average molecular weight. The apparent sizes of the conjugates of the invention must reflect to some extent the variation in the molecular weights of the PEG molecules that are used to make the conjugates.

In addition, the level of precision in the art of apparent size measurement (which is determined by size exclusion chromatography as defined on page 25, lines 13-22 of the specification) is significantly lower than the level of precision in the art of length measurement. Therefore, the need to use the term "about" to describe the apparent size parameters of the present invention is even greater than the need to use the term "about" to describe the length parameters of the Modine Manufacturing invention. Given the variability

inherent in the apparent size elements of Applicants' invention, the law requires no more precision in claiming the apparent size elements than that employed in the present claims.

In view of the claim amendments and the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Double Patenting Rejection

The Office provisionally rejects claims 1, 5, 8, 10, 15, 18, 19, 21, 24-26 and 28-35 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 5, 8, 10, 15, 18, 19, 23, 26, 27, 29 and 30 of copending application U.S. Ser. No. 09/012,116. Application U.S. Ser. No. 09/012,116 is now abandoned. Since the provisional rejection is moot, Applicants respectfully request that it be withdrawn.

Rejection under 35 U.S.C. §102(e) based on Faanes

Claims 1, 5, 10, 18, 19, 30, 31 and 32 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Pat. No. 5,695,760 to Faanes, et al., hereafter "Faanes." The Office apparently finds that Faanes disclosed a conjugate comprising an antibody covalently conjugated to no more than 10 PEG molecules which can be up to 40 kD each, wherein the apparent size of the conjugate is at least 500 kD.

Without intending acquiescence to the rejection, but rather to expedite prosecution, Applicants have amended claim 1 (and necessarily also claims 5, 19, 21, 26, 28, 29 and 31-35 depending therefrom) to recite a Fab' antibody fragment that is derivatized with PEG only through the covalent attachment of PEG to a cysteine residue in one chain that would be in a disulfide bridge with a corresponding cysteine residue in the opposite chain but for substitution of the corresponding cysteine residue with another amino acid residue. Thus, the amended claims are directed to PEGylation at a unique site in the Fab' molecule that is created by the replacement of a native cysteine residue with another amino acid residue in the molecule.

To anticipate a claim in a patent application, a prior art reference must teach every element of the claim (MPEP 2131). Faanes does not teach or suggest the creation of a unique PEGylation site through the replacement of a native cysteine residue with another amino acid residue in any of the enlimomab (anti-ICAM monoclonal antibody)-PEG conjugates of Faanes. Since Faanes did not provide the unique PEGylation site specified in the claims, Faanes does

not anticipate the claimed invention.

In view of the present claim amendments and the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of the §102(e) rejection based on Faanes.

Rejection under 35 U.S.C. §102(e) based on Application U.S. Ser. No. 09/012,116

Claims 1, 5, 8, 10, 15, 18, 19, 21, 24-26 and 28-35 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by the disclosure of Application U.S. Ser. No. 09/012,116. As noted above, Application U.S. Ser. No. 09/012,116 is now abandoned. Since Application U.S. Ser. No. 09/012,116 fails to qualify as a §102(e) reference against the claims, Applicants respectfully submit that the §102(e) rejection based on Application U.S. Ser. No. 09/012,116 should be withdrawn.

Rejection under 35 U.S.C. §102(f)

Claims 1, 5, 8, 10, 15, 18, 19, 21, 24-26 and 28-35 are rejected under 35 U.S.C. §102(f) as allegedly being anticipated by Application U.S. Ser. No. 09/012,116.

The rejection is apparently based on the fact that the inventorship named in Application U.S. Ser. No. 09/012,116 differs slightly from the inventorship named in the present application. The difference is that Iphigenia Koumenis is included in the named inventorship of the present application but is not included in the originally named inventorship of Application U.S. Ser. No. 09/012,116. The omission of Iphigenia Koumenis from the originally named inventorship of Application U.S. Ser. No. 09/012,116 was due to an inadvertent oversight on the part of Applicants. Applicants attempted to correct this oversight by petition for correction of inventorship, but the Office denied the petition because it allegedly contained some formal defects. Since Applicants intended to allow Application U.S. Ser. No. 09/012,116 to go abandoned, Applicants did not attempt to submit another petition for correction of inventorship in Application U.S. Ser. No. 09/012,116.

Despite the fact that the named inventorship of record in Application U.S. Ser. No. 09/012,116 still erroneously omits Iphigenia Koumenis, it should be apparent from the record that the inventorship of the disclosure of Application U.S. Ser. No. 09/012,116 is identical to the inventorship of the present application. In parent application U.S. Ser. No. 60/074,330, the named inventorship was properly corrected by petition to add Iphigenia Koumenis as a co-inventor of the subject matter disclosed and claimed in that application (see the Petition for Correction of Inventorship filed on November 6, 1998 and the Decision on Petition dated

November 13, 1998 in parent application U.S. Ser. No. 60/074,330). The disclosure and claims of parent application U.S. Ser. No. 60/074,330 are identical to the disclosure and claims of the reference Application U.S. Ser. No. 09/012,116. In addition, parent application U.S. Ser. No. 60/074,330 and reference Application U.S. Ser. No. 09/012,116 were filed on the same day, January 22, 1998. Thus, the file history of the present application is sufficient to demonstrate that the inventorship of the disclosure of the reference Application U.S. Ser. No. 09/012,116 is the same as the inventorship named in the present application.

In view of the above, Applicants submit that the inventors named in the present application also invented the subject matter disclosed in the reference Application U.S. Ser. No. 09/012,116. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(f).

Rejection under 35 U.S.C. §103(a) based on Braxton, Doerschuk, Delgado and Griffiths.

Claims 1, 5, 8, 10, 15, 18, 19, 21, 26, 28, 29 and 30-35 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Pat. No. 5,766,897 to Braxton, hereafter "Braxton," in view of U.S. Pat. No. 5,702,946 to Doerschuk, et al., hereafter "Doerschuk," Delgado, et al., Brit. J. Cancer, 73: 175-182, 1996), hereafter "Doerschuk," and U.S. Pat. No. 5,670,132 to Griffiths, et al., hereafter "Griffiths." The Office finds that Braxton taught immunoglobulins conjugated to PEG molecules from about 0.2 kD to 20 kD in size, Doerschuk taught anti-IL-8 antibodies and Fab' antibody fragments, Delgado taught the PEGylation of proteins to achieve increased plasma half-life, increased resistance to proteolysis, and substantial reduction in antigenicity/immunogenicity, and Griffiths taught a labeled Fab'-PEG conjugate possessing faster targeting kinetics and a lower rate of immune response induction than intact IgG molecules, for use as an in vivo diagnostic. The Office apparently concludes that it would have been obvious to substitute the anti-IL-8 Fab' fragments of Doerschuk in place of immunoglobulin in the PEGylated conjugates taught by Braxton in order to achieve the increased plasma half-life, increased resistance to proteolysis, and substantial reduction in antigenicity/immunogenicity of PEGylated proteins taught by Delgado and the faster kinetics and lower immune response induction rate for a Fab–PEG conjugate taught by Griffiths.

Without intending acquiescence to the rejection, but rather to expedite prosecution, Applicants have amended claim 1 (and necessarily also claims 5, 19, 21, 26, 28, 29 and 31-35 depending therefrom) to recite a Fab' antibody fragment that is derivatized with PEG only

through the covalent attachment of PEG to a cysteine residue in one chain that would be in a disulfide bridge with a corresponding cysteine residue in the opposite chain but for substitution of the corresponding cysteine residue with another amino acid residue. Thus, the amended claims are directed to PEGylation at a unique site in the Fab' molecule that is created by the replacement of a native cysteine residue with another amino acid residue in the molecule.

Braxton does not teach or suggest the creation of a unique PEGylation site through the replacement of a native cysteine residue with another amino acid residue in any of the protein-PEG conjugates of Braxton. Delgado only describes the use of secondary amine coupling (a non-site specific technique) for the derivatization of Delgado's Fab' fragments with PEG. Likewise, Griffiths contains no description that would have led the practitioner to employ the unique PEGylation site in an antibody fragment as claimed herein. Finally, Doerschuk does not even mention PEGylation of the anti-IL-8 antibody fragments described in Doerschuk. Since nothing in the cited references would have provided the practitioner with the unique PEGylation site recited in the claims, the claimed invention is patentable over any combination of Braxton, Doerschuk, Delgado and Griffiths.

In view of the claim amendments and the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of the §103(a) rejection based on Braxton, Doerschuk, Delgado and Griffiths.

Rejection under 35 U.S.C. §103(a) based on Faanes and Doerschuk

Claims 1, 5, 8, 10, 15, 18, 19, 26, 28, 29 and 30-35 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Faanes in view of Doerschuk. The Office apparently finds that Faanes disclosed a conjugate comprising an antibody covalently conjugated to no more than 10 PEG molecules which can be up to 40 kD each, wherein the apparent size of the conjugate is at least 500 kD, and disclosed that PEG modification of antibody/antibody fragments confers the benefits of extended half-life and reduced immunogenicity in human therapeutic applications. The Office reiterates its finding that Doerschuk taught anti-IL-8 monoclonal antibodies and Fab' antibody fragments. The Office apparently concludes that it would have been obvious to create the claimed invention by substituting the anti-IL-8 Fab' of Doerschuk in place of the immunoglobulin in the conjugate of Faanes. In particular, the Office contends that the practitioner would have been motivated to PEGylate the anti-IL-8 Fab' of Doerschuk according to the teachings of Faanes in order to achieve the extended half-life and

reduced immunogenic properties of the conjugates described in Faanes.

Without intending acquiescence to the rejection, but rather to expedite prosecution, Applicants have amended claim 1 (and necessarily also claims 5, 19, 21, 26, 28, 29 and 31-35 depending therefrom) to recite a Fab' antibody fragment that is derivatized with PEG only through the covalent attachment of PEG to a cysteine residue in one chain that would be in a disulfide bridge with a corresponding cysteine residue in the opposite chain but for substitution of the corresponding cysteine residue with another amino acid residue. Thus, as noted above, the amended claims are directed to PEGylation at a unique site in the Fab' molecule that is created by the replacement of a native cysteine residue with another amino acid residue in the molecule.

Faanes does not teach or suggest the creation of a unique PEGylation site through the replacement of a native cysteine residue with another amino acid residue in any of the enlimomab (anti-ICAM monoclonal antibody)-PEG conjugates of Faanes. Doerschuk does not even mention PEGylation of the anti-IL-8 antibody fragments described in Doerschuk. Since nothing in the cited references would have provided the practitioner with the unique PEGylation site recited in the claims, the claimed invention is patentable over any combination of Faanes and Doerschuk.

In view of the claim amendments and the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of the §103(a) rejection based on Faanes and Doerschuk.

Rejection under 35 U.S.C. §103(a) based on Faanes, Doerschuk and Griffiths

Claims 21, 24 and 25 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable Faanes and Doerschuk as applied to claims 1, 5, 8, 10, 15, 18, 19, 26, 28, 29 and 30-32 in the previous rejection, and further in view of Griffiths. The Office finds that while Faanes did not teach radiolabeled conjugates, Griffiths taught a radiolabeled Fab'-PEG conjugate and its use as an in vivo diagnostic. The Office apparently concludes that it would have been obvious to use the radiolabeling taught by Griffiths to modify the anti-IL-8 Fab'-PEG conjugate taught by the combination of Faanes and Doerschuk. In addition, the Office concludes that it would have been obvious to employ art-known PEG's, such as straight chain PEG's, in any such conjugate and to make the conjugate free of other matter in order to insure purity and potency of the conjugate for therapeutic use.

Claims 24 and 25 are canceled herein. Thus, the rejection is moot with respect to these

claims.

Without intending acquiescence to the rejection, but rather to expedite prosecution, Applicants have amended claim 1 (and necessarily also claims 5, 19, 21, 26, 28, 29 and 31-35 depending therefrom) to recite a Fab' antibody fragment that is derivatized with PEG only through the covalent attachment of PEG to a cysteine residue in one chain that would be in a disulfide bridge with a corresponding cysteine residue in the opposite chain but for substitution of the corresponding cysteine residue with another amino acid residue. Thus, as noted above, the amended claims are directed to PEGylation at a unique site in the Fab' molecule that is created by the replacement of a native cysteine residue with another amino acid residue in the molecule.

Faanes and Doerschuk fail to teach or suggest the unique PEGylation site recited in the claims, as shown above. In addition, Griffiths contains no description that would have led the practitioner to employ the unique PEGylation site in an antibody fragment. Since nothing in the cited references would have provided the practitioner with the unique PEGylation site recited in the claims, the claimed invention is patentable over any combination of Faanes, Doerschuk and Griffiths.

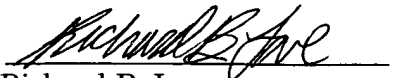
In view of the claim amendments and the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of the §103(a) rejection based on Faanes, Doerschuk and Griffiths.

In light of the above, Applicants respectfully submit that the application is in condition for allowance and earnestly solicit a Notice to that effect. If the Examiner has any question concerning this response, the Examiner should not hesitate to contact the undersigned attorney at the telephone number indicated below.

Respectfully submitted,

GENENTECH, INC.

Date: November 22, 2000

By: 

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